Journal Club: The Use of Fish Oil Lipid Emulsion for Gastrointestinal Surgery Patients

Introduction/Background

I. Surgical Patients
   a. Surgical patients have a greater risk of complications due to depressed cellular and humoral immune function as a result of the underlying disease

II. Fatty acids
   a. Long-chain omega-6 PUFA are precursors of potentially inflammatory eicosanoids
   b. Excess omega-6 rises the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) both of which are eicosanoids that can cause cell death
   c. SO emulsions can impair immune function by decreasing lymphocyte proliferation and leading to neutrophil and lymphocyte apoptosis and necrosis

III. Immune Response
   a. EPA and DHA can directly or indirectly influence immune response
      i. Positively affect the production of eicosanoids
         1. Derived from omega-3 or omega-6 - has complex control over inflammation – pro-inflammatory
      ii. Positively affects production of cytokines
         1. Aids cell-to-cell communication in immune responses
      iii. Positively affects production of resolvins
         1. Reduce cellular inflammation by inhibiting the production and transportation of inflammatory cells and chemicals to the site of inflammation
   b. Parenteral infusion of fish oil lipid emulsions avoids digestive and absorptive losses of omega-3 PUFA compared to oral and enteral routes
      i. Allows for faster incorporation of omega-3 PUFAs in plasma and blood cells
      ii. In healthy individuals it was found that there was a reduction in the release of pro-inflammatory cytokines
         1. This suggests a fast immune-modulatory effect

Parenteral fish oil as a pharmacological agent to modulate post-operative immune response: A randomized, double-blind, and controlled clinical trial in patients with gastrointestinal cancer
I. Introduction
   a. Benefits of fish oil containing lipid emulsions
      i. Better post-operative balance of inflammatory mediators
      ii. Decrease in post-operative infection rates
      iii. Decreased length of stay
   b. Majority of surgical patients would not benefit because currently only used for those who cannot meet nutritional needs orally
   c. Proposal: using fish oil lipid emulsions independently of PN therapy
   d. Goal of study: Assess the effect of peripheral infusion of parenteral fish oil LE as a pre-operative pharmacological agent on the post-operative immune response and its impact on clinical outcomes of patients with gastrointestinal cancer.

II. Materials and Methods
   a. Patients
      i. Inclusion criteria
         1. 18-75 years old admitted to the gastrointestinal surgery division
         2. Elective surgery for removal of gastric or colon cancer
         3. Karnofsky score >/ 60
            a. Score of 0-100 (100 being perfect health and 0 being death)
            b. Used to evaluate cancer patient’s predicted ability to survive chemotherapy
         4. Suitable peripheral venous access
      ii. Exclusion criteria
         1. Allergy to any ingredient of the LE
         2. Inflammatory disease (ex: arthritis)
         3. Metabolic disease (ex: insulin-dependent diabetes)
         4. Immunological disease (ex: lupus)
         5. Dementia or other cognitive and behavioral problems
   b. LE treatment
      i. Experimental group: fish oil - Omegaven 10%
      ii. Control group: Lipovenos MCT 10% (MCT/LCT)
      iii. Three days prior to surgery: 0.2 g/kg of LE was infused 6 hr/day
   c. Immune response analysis
      i. Blood collections: before LE, after LE, and POD#3
      ii. Interleukin samples were collected POD#6
   d. Inflammatory mediators
      i. IL-6: produced at the site of inflammation (proinflammatory) – plays a key role in acute phase response
1. When combined with its soluble receptor it dictates the transition from acute to chronic inflammation
   ii. IL-10: limits and terminates inflammatory responses and regulates differentiation and proliferation of immune cells
   iii. CRP: measurement of general level of inflammation – regulated by IL-6
   iv. Prostoglandin E2: modulates inflammation and enhances its own production by suppressing acute inflammatory mediators

e. Leukocyte function
   i. AKA white blood cells – cells of the immune system that depend the body
   ii. HLA-DR: human leukocyte antigen cell-surface receptor

f. Clinical outcomes
   i. End point: post-operative clinical outcomes
   ii. Additional risk of complications (elderly and malnourished)

III. Results
   a. Patients
      i. 63 completed infusion protocol (FO 31 & MCT/LCT 32)
         1. 2 MCT/LCT patients died post-op
   b. Immune response
      i. IL-6 levels: FO observed a decrease and MCT observed an increase from baseline
         1. Suggesting FO LE induced favorable post-operative physiological modulation (increase on POD3 and decrease on POD6)
      iii. HLA-DR and CD32: fish oil LE preserved these leukocyte phenotype markers and reduced the negative impact on burst function
         1. A decrease in these numbers indicates the functional deactivation of these leukocytes which is a central marker for immune paralysis after surgical trauma
         2. This suggests that pre-operative infusion of fish oil may contribute to improved clinical outcomes
   c. Clinical outcomes
      i. No significant difference in the frequency of infectious complications (no difference in subgroups of elderly and malnourished)
      ii. Elderly and malnourished patients receiving MCT/LCT had a significantly higher variation in the length of ICU stay than those receiving FO

IV. Discussion
   a. Was found to favorably modulate post-operative immune mediators
b. Infusion protocol was safe and well tolerated, with mild adverse effects which disappeared without LE treatment interruption

c. Optimal timing of infusion is still undetermined — emerging evidence suggest pre-operative window is more effective

d. MCT are found to have a neutral impact as they are not susceptible to peroxidation and don’t directly participate in eicosanoid synthesis

e. Reference additional study: Soybean oil LEs are rich in omega-6 FA which are potentially inflammatory and immunosuppressive

f. Limitations
   i. Nutritional status was not taken into account during selection
   ii. The basal levels of IL-6 and IL-10 were different amounts the two groups

V. Conclusion
   a. Pre-operative infusion of fish oil may reduce immune dysfunction after surgical trauma

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**Human leukocyte death after a preoperative infusion of medium/long-chain triglyceride and fish oil parenteral emulsions: a randomized study in gastrointestinal cancer patients**

I. Introduction
   a. Interleukin-6 (pro-inflammatory cytokine) is released during surgery and can induce leukocyte apoptosis and as a result impair immune function
   b. Leukocyte antigen HLA-DR and lymphocyte distribution and proliferation was preserved with FO emulsions
      i. This prevented post-operative drop in an interferon release, increased IL-2, tumor necrosis factor, and IL-2R
   c. Purpose: to assess whether positive findings regarding MCT/LCT and FO emulsions on leukocyte functions and counts in surgical patients are associated with a possible protective effect on leukocyte death, the impact on cell viability, apoptotic markers, and expressions of genes associated with cell death

II. Materials and Methods
   a. Patient Selection
      i. 25 patients randomly selections from surgical patients with stomach or colon cancer
      ii. Inclusion criteria
         1. 37-75 years old
         2. Karnofsky score >/ 60
      iii. Exclusion criteria
1. Intolerance or allergy to LE ingredients, diagnosis of infection, inflammatory, immunologic, or metabolic diseases

b. Lipid emulsion protocol
   i. Control group: Lipovenous MCT 10%
   ii. Experimental group: Omegavenos 10%
   iii. Infusion 3 days prior to surgery at 0.2 g/kg x 6hrs

c. Cell Isolation
   i. Blood samples were collected on at the end of the infusion and on POD#3
   1. They were analyzed for leukocyte death

III. Results

a. Patients
   i. There were no differences in age, gender, type of tumor, nutritional status, type of open surgery, or comorbidities between the two groups

b. Leukocyte death
   i. MCT emulsions tripled the proportion of cells with DNA fragmentation
   ii. Fish oil emulsion reduced the relative proportion of viable cells by 7%, reduced the percentage of cells with phosphatidylserine externalization by 74%, and had no effect on cell DNA fragmentation or mitochondrial depolarization
      1. Viable cells: ability to live on their own
      2. Phosphatidylserine externalization: phospholipid component usually on the inner-leaflet of the cell membrane. When undergoing apoptosis it is no longer restricted to the inside and becomes externalized
      3. DNA fragmentation: a key feature of apoptosis
      4. Mitochondrial depolarization: during cell destruction the inner membrane losses its membrane potential
   iii. There was no difference in lymphocyte or neutrophil death when MCT/LCT and FO was compared during either pre- or postoperative

c. Gene expression
   i. Total of 108 genes that are related to cell death
      1. MCT/LCT altered the expression of 12 genes
         a. Upregulated the expression of 7 genes related to cell death and 2 related to cell proliferation
            i. Increasing the cellular response to a stimulus due to an increase in surface receptors
         b. Downregulated the expression of 3 genes related to cell death
i. Decreasing the response to a stimulus

2. FO modulated the expression of 7 genes
   a. Upregulated the expression of 3 genes related to cell death and 2 genes related to cell proliferation
   b. Downregulated the expression of 2 genes related to cell death

IV. Discussion
   a. MCT/LCT infusion didn’t modify neutrophil or lymphocyte death but may induce postoperative apoptosis if these leukocytes, as indicated by the increased proportions of cells with PS externalization or DNA fragmentation
   b. Major tissue injury (such as surgery) leads to production of pro-inflammatory cytokines which creates a cell-detrimental environment
      i. The increase of postoperative lymphocyte and neutrophil apoptosis could possibly be a result of the modifications induced by surgical trauma rather than from the pro-apoptotic effect of the LE
   c. The FO emulsion did not chance cell apoptosis however it was found that FO has a protective effect on postoperative lymphocyte apoptosis by substantially decreasing the proportion of leukocytes with PS externalization
   d. MCT/LCT infusion induced postoperative leukocyte cell death whereas FO didn’t
      i. Can be associated with preactivation of pro-apoptotic pathways
      ii. However can also be associated with the inhibition of pro-apoptotic genes
      iii. This suggests that there may be a possible apoptosis regulatory mechanism which makes it hard to exclude the influences of other physiological factors related to surgery
   e. FO demonstrates a clear protective effect on postoperative lymphocyte death by downregulating pro-apoptotic and upregulating anti-apoptotic genes

V. Conclusion
   a. In patients with gastrointestinal cancer, the preoperative infusion of MCT’LCT is associated with postoperative lymphocyte and neutrophil apoptosis, whereas FO has a protective effect on postoperative lymphocyte apoptosis

Superiority of fish oil-enriched emulsion to medium-chain triacylglycerols/long-chain triacylglycerols in gastrointestinal surgery patients: a randomized clinical trial

I. Introduction
a. Previous studies have suggested that fish oil-enriched PN can ameliorate infections and reverse PN-related cholestasis

b. Purpose: to assess the safety and efficacy of parenteral emulsions of fish oil and MCT/LCT after gastrointestinal surgery

II. Materials and Methods

a. Patients
   i. 64 patients with gastrointestinal diseases
      1. 18-85 years old
      2. Exclusion: hyperlipidemia, diabetes, pregnancy, hyperthyroidism, hepatic dysfunction, BMI lower than 18.5 or higher than 28, immunologic deficiencies, coagulation disorders, or severe heart or renal disease
   ii. Received TPN with either fish oil or MCT/LCT for 5 days postop

b. Nutritional Regimen
   i. Experimental group: Lipopuls 20% (10% fish oil)
   ii. Control group: Lipofundin 20% (50% MCT; 50% SO)
   iii. 0.8 g/kg lipids were given for 5 days with half dose given on first day

c. Inflammatory Parameters
   i. Multiple plasma inflammatory cytokines were analyzed

III. Results

a. Clinical outcomes
   i. Combination of gastric cancer, colon cancer, and other various digestive diseases
   ii. Infectious complications and incidence of systemic inflammatory response syndrome were seen less with the experimental group however with no significance

b. Laboratory
   i. T-bili was significantly decrease in the experimental group whereas the control group saw an increase
   ii. Activated partial thromboplastin time (APTT) is a measurement of coagulation – this was prolonged with the experimental group compared to the control implicating a potential anticoagulant effect of fish oil during the early part of postop

c. Inflammatory biomarkers
   i. LTB5/LTB4 (leukotriene – eicosanoid inflammatory mediator which regulate immune response) increased in the experimental group and decreased in the control which is a critical anti-inflammatory indicator
ii. CRP and TNF (tumor necrosis factor – cytokine that can cause apoptosis) increased in both groups until day 3 and then decreased

iii. At study conclusion, the experimental group saw a decrease in IL-6 and significantly reduced the increase in LTB5/6, TNF, and NF-kB (nuclear factor kappa B – protein complex that is involved in cellular responses - incorrect regulation has been linked to inflammation)

IV. Discussion
   a. Based on the findings with a decrease in APTT it is advisable that caution be taken when providing TPN with fish oil to patients with coagulation disorders
   b. In previous studies it was found that MCT was superior to soybean oil in improving immunologic function and decreased postoperative complications however no significant difference was seen between MCT and fish oil
   c. It is reasonable to speculate that fish oil might inhibit the release of inflammatory mediators by sustaining the activity of NF-kB
   d. Limitations:
      i. Small sample size which decreases the accuracy
      ii. Duration of intervention may have been too short to observe reverse-cholestasis

V. Conclusion
   a. The use of fish oil after gastrointestinal surgery was safe and well tolerated
   b. The efficacy of fish oil in restoring liver function was observed even during the short-term administration
   c. Fish oil was superior in modulating the excessive inflammatory response by inhibiting the release of multiple pro-inflammatory biomarkers